



Associations of childhood allergies with parental reproductive and allergy history

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Abstract

Purpose There has been a noted parallel rise in both the use of Assisted Reproductive Technology (ART) to conceive and childhood allergies in the last few decades. The purpose of this study was to investigate the possible association between reproductive and allergy history in parents and allergies in their children.

Methods This exploratory study used a cross-sectional study design and web-based survey to collect anonymous data on demographics, allergy, and health history from parents and about each of their children under 18 years of age. Children were stratified into two groups by allergy status (yes/no), and associations between each variable and the odds of allergies were tested using univariable and multivariable mixed logistic regression models.

Results Of the 563 children in the study, 237 were reported to have allergies whereas 326 did not. Age, residential community, household income, mode of conception, paternal age at conception, biological parental allergy status, and history of asthma and eczema were significantly associated with allergies in univariable analysis. Multivariable analysis revealed household income (\$50 k to \$99 k vs $\geq$ \$200 k adj OR = 2.72, 95% CI 1.11, 6.65), biological parental allergies (mother-adj OR 2.74, 95% CI 1.59, 4.72, father-adj OR 2.06, 95% CI 1.24, 3.41) and each additional year of age of children (adj OR 1.17, CI 1.10, 1.24) were significantly associated with odds of allergies in children.

Conclusion Although the exploratory nature of this convenience, snowballing sample limited the generalizability of the findings, initial observations warrant further investigation and validation in a larger more diverse population.

Keywords Allergy · Parental reproductive health history · Children · Assisted reproductive technology · Mode of conception

Introduction

Allergies are defined by an IgE-mediated immune reaction to a typically harmless antigen and are most prevalent in children [1, 2]. Around 8% of children in the US alone are thought to be impacted by allergies, and over the past few decades, allergy incidence has increased globally in children under the age of 18 [3]. In fact, food allergy prevalence in children has increased from 3.4% in 1997–1999 to an estimated 5.8% in 2021 [4, 5]. With allergic reactions ranging from mild to potentially life-threatening and the direct medical costs of allergies totaling over \$4.3 billion annually, allergies have become a major public health crisis [6, 7]. The exact cause of this rise in allergy incidence is still largely unknown, but leading hypotheses include changes in hygiene practices, diet, environmental pollution, and intestinal microbial communities [8–11].

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Specific parental factors may also be associated with allergies in children, including parental allergies, obesity, and metabolic disorders [12–14]. More recently parental reproductive health factors have been found to be associated with allergy development in children, including parental age at time of conception [15, 16]. Children conceived to mothers of advanced reproductive age had a higher odds of allergic conditions, while younger paternal age at the time of conception was associated with a higher incidence of asthma in children [15, 16]. Maternal health and specific pregnancy complications have also been associated allergy incidence in offspring, with women suffering from preeclampsia and chronic stress during pregnancy having offspring with an increased incidence of allergic wheezing and asthma [17, 18]. In addition, recent studies have investigated the association between assisted reproductive technologies (ART) use and allergies in children. ART are procedures used to treat male and female infertility with the ultimate goal of achieving a live birth [19]. Children conceived using ART, including in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), had an altered immune system, with elevated levels of cytokines that contribute to allergic diseases [20]. Children conceived using ART had an increased odds of allergic sensitization, and children conceived using IVF or ovulation induction/intrauterine insemination (OI/IUI) were more likely to develop asthma or other allergic conditions [21, 22]. These data reveal that parental reproductive health factors may have an important influence on allergies in children.

Despite the parallel rise in infertility rates, ART use, and allergy incidence in children, it is still largely unknown how parental reproductive health impacts allergy trends in children [23–26]. Therefore, we performed an exploratory study to gain additional insight into how parental allergy status and reproductive factors, including infertility and ART use, may be associated with allergy history in children.

Methods

Study design

Given the paucity of literature in this particular area of study, this exploratory research used a cross-sectional study design to explore the possible association between allergy and reproductive health characteristics in parents and allergies in their children. A convenience sample using snowball sampling was used to capture a wider representation of the general public given the exploratory nature of this research, the lack of formal funding, and the goal of generating hypotheses for future follow-up studies. Individuals were excluded from responding to the survey if they were less than 18 years old or did not have a child

under 18 years old. The limitations on the age of the child being reported were designed to help minimize recall bias, while including the span of childhood for possible allergy history. No compensation was provided for participation in the study. Data were obtained from adults over 18 years old who had children under the age of 18 following informed consent through an Institutional Review Board approved study.

The survey instrument was created in SurveyMonkey due to its more advanced skip logic capabilities, beyond the functionality available in RedCap, while identifying information was not collected and responses were anonymous. The survey instrument consisted of questions that were a combination of quantitative multiple-choice, qualitative free-response, and mixed methods (Supplemental Material 1). The survey contained a total of 17 questions followed by an additional 28 questions for the respondent to answer about each child under the age of 18. For the respondent, sociodemographic questions collected information regarding age, sex, ethnicity, community the respondent lives in, household income, and highest degree received. Allergy specific questions collected information regarding respondent's specific environmental, food and drug allergies, and food sensitivities. Questions about the respondent's children assessed how many children lived in their household and what environment their children typically lived in. Reproductive health data included information on the number of previous live births and miscarriages the respondents and their partner had, the age at which the respondent started puberty, and whether they have ever been diagnosed with a reproductive condition.

For each child under the age of 18, background questions collected data on the child's sex, age, birth year, race, vaccination status, and whether the child had been diagnosed with eczema, asthma, or an autoimmune condition. Allergy related variables included information on the types of allergies the child and their biological mother and father had, the age at which the child was diagnosed with a food allergy, the number of sensitizing treatments the child had undergone (if applicable), and number of anaphylactic reactions. Reproductive health data included whether the respondent was the child's biological parent, if the child was adopted, mode of conception, use of ART, if the child was conceived using donor eggs, sperm, or embryos, reproductive history of pregnancies and births, and history of reproductive conditions. Prenatal and neonatal questions collected information on the age of the biological parents at the time of conception, length of conception, mode of conception (spontaneously, IVF, intrauterine insemination (IUI), ICSI), and mode of delivery. Neonatal data included prematurity at birth (including weeks of prematurity and time in NICU), birth or pregnancy complications, length of time breastfed, and any allergies to breastmilk or a component of breastmilk.

Survey dissemination

The survey was distributed via a convenience snowball sampling method from October 2020 to March 2021. The online survey was promoted and shared through social media as well as through university listservs (Supplementary Material 2). Through multiple waves of recruitment and marketing every effort was made to increase exposure and awareness of the study at multiple points throughout the recruitment window. Special interest groups were targeted, including parent groups, reproductive interest groups, women's health interest groups, food allergy support groups, eczema support groups, and children's health interest groups, support groups for mothers of color, equity groups, LGBTQ+ parent groups, former fertility patient support groups, and Chicago parent support groups (Supplementary Material 3). In addition, the survey was shared with relevant professional societies including the European Society of Human Reproduction and Embryology, the Society for the Study of Reproduction, the American Society for Reproductive Medicine, and the Asia Pacific Initiative on Reproduction. Due to the anonymous nature of the survey, we could not track where/how individuals accessed the survey.

Statistical analysis

Summary statistics were calculated including relative frequencies for all categorical variables and means and standard deviations for all numeric variables. The following variables were identified as needing aggregation of some categories due to sparsity of data: household income, parental education, length of time breastfed, and types of ART used. All subsequent analysis used aggregated categories. Associations between each explanatory variable and the odds of allergies were tested using univariable Generalized Linear Mixed Models (GLMM) in the form of a separate mixed logistic regression for each explanatory variable with a random intercept for household in the lme4 package in R [27]. Open-ended responses for allergies in children and in parents were compared with quantitative responses to identify discrepancies in responses. When qualitative responses yielded allergies that were not selected in the quantitative previous section, the quantitative selection was imputed based on qualitative data. For example, if a respondent did not select dairy allergies in the multi-select quantitative boxes, but then reported "dairy" in the open-ended responses, "dairy" was imputed in the quantitative boxes. Qualitative data on allergies was collected with two questions: "Do you have any diagnosed allergies?" with "other (please specify)" as the open-ended text prompt and "Of the types of allergies you listed above, what specifically are you allergic to:" with separate fields for open-ended text entry for food allergies,

environmental allergies, medicine, food sensitivities (not allergies) and unknown.

To test whether univariable associations remained after adjusting for sociodemographic and reproductive and health history characteristic, we ran a full multivariable GLMM in the form of mixed logistic regression with a random intercept for household. As an initial exploratory study, there was not sufficient established studies to provide necessary context to guide model reduction. Exposures of interest included ART, breast-feeding, breast-feeding allergies, mode of delivery, mother allergy status, father allergy status, and vaccination status. Multivariable GLMM results were also adjusted for income, age of child, sex, parental education, race, and community. Variance inflation factors (VIF) were checked for the full model and no evidence of multicollinearity was found. Responses with missing data were excluded from the associated analyses. All statistical analysis were performed in R, version 4.0.2 [28].

Results

Demographic characteristics of children in the study population

A total of 340 parents from separate households responded to the survey with a total of 563 children. Of the 563 children reported by respondents, 237 children had at least one kind of allergy while 326 children had no reported allergy. Children in our study on average were 6.8 years of age ($SD = 4.9$), were male, white (68.98%), residing in suburban community settings (62.92%), from a household with $\geq \$200$ k annual income (43.34%), and had a parent with a graduate degree (69.27%). The odds of allergies were higher among children who were older in age ($OR = 1.17$, 95% CI: 1.11, 1.23) and living in a suburban as opposed to an urban environment ($OR = 2.38$, 95% CI: 1.34, 4.24) (Table 1). Household income was also significantly associated with allergies in children ($OR = 0.47$, 95% CI: 0.23, 0.97) (Table 1). Those children who lived in a household with a reported annual income of \$100,000 to \$149,999 had significantly lower odds of allergies than those with an annual income of $\geq \$200,000$ k (Table 1).

Allergy history

Among the 43.95% of children in our study who were reported to have allergies, the most prevalent were: hay fever (24.02%), peanut (12.10%), pets (10.68%), tree nuts (10.68%), milk (7.65%), and eggs (7.30%). Respondents reported at least one allergy for 63.59% of the biological mothers and 53.48% of the biological fathers, the most common of which were: hay fever, pets, medicine, and mold with prevalence as much as

Table 1 Demographic characteristics of the children in the study population by allergy status

Characteristic	Allergies n/N (%)	No-Allergies n/N (%)	OR (95% CI) ^a
Sex			
Male	119 / 237 (50.21%)	166 / 326 (50.92%)	— ^b
Female	115 / 237 (48.52%)	155 / 326 (47.55%)	0.99 (0.63, 1.54)
Other	3 / 237 (1.27%)	5 / 326 (1.53%)	0.71 (0.10, 5.27)
Mean Age in years (SD)	8.43 (4.9, <i>n</i> = 235)	5.62 (4.6, <i>n</i> = 326)	1.17 (1.11, 1.23)
Race			
Asian Am/PI/AI/AN	21 / 236 (8.90%)	16 / 326 (4.91%)	2.11 (0.78, 5.72)
Black	7 / 236 (2.97%)	20 / 326 (6.13%)	0.37 (0.11, 1.29)
White	156 / 236 (66.10%)	231 / 326 (70.86%)	— ^b
Unknown/NS	0 / 236 (0.00%)	1 / 326 (0.31%)	— ^c
Multiple	52 / 236 (22.03%)	58 / 326 (17.79%)	1.42 (0.75, 2.68)
Community			
Suburban	164 / 235 (69.79%)	189 / 326 (57.98%)	2.38 (1.34, 4.24)
Urban	50 / 235 (21.28%)	111 / 326 (34.05%)	— ^b
Rural	21 / 235 (8.94%)	26 / 326 (7.98%)	1.85 (0.70, 4.90)
Household Income ^d			
\$0-\$49,999	11 / 237 (4.64%)	18 / 326 (5.52%)	0.81 (0.24, 2.69)
\$50,000-\$99,999	36 / 237 (15.19%)	31 / 326 (9.51%)	1.81 (0.82, 3.99)
\$100,000-\$149,999	31 / 237 (13.08%)	73 / 326 (22.39%)	0.47 (0.23, 0.97)
\$150,000-\$199,999	42 / 237 (17.72%)	54 / 326 (16.56%)	1.11 (0.55, 2.23)
\$200,000 and up	100 / 237 (42.19%)	144 / 326 (44.17%)	— ^b
Would rather not respond	17 / 237 (7.17%)	6 / 326 (1.84%)	5.68 (1.49, 21.68)
Parental Education ^e			
Less than a bachelor's degree	17 / 237 (7.17%)	18 / 326 (5.52%)	— ^b
Bachelor's degree	53 / 237 (22.36%)	83 / 326 (25.46%)	0.66 (0.26, 1.71)
More than a bachelor's degree	167 / 237 (70.46%)	223 / 326 (68.40%)	0.81 (0.34, 1.95)
Would rather not respond	0 / 237 (0.00%)	2 / 326 (0.61%)	— ^f

a. Odds ratios (OR) and 95% confidence intervals (CI) calculated from a separate univariable Generalized Linear Mixed Model (GLMM) for each characteristic in the table. Each univariable GLMM was run as a mixed logistic regression model with a random intercept for household

b. Reference category

c. One child with unknown race was excluded from modeling

d. Nested model test for income had a *p*-value of 0.004

e. Parental education was self-reported highest attained education of the respondent

f. Two children with unknown parental education were excluded from modeling

2.6 times higher in biological mothers as compared to fathers (Table 2). Of the 134 children for which responses were made to questions regarding sensitizing treatments and anaphylactic reactions, 89.55% of children had never received sensitizing treatments, while 10.45% were reported to be currently receiving them. A majority of children with a reported allergy had never had an anaphylactic reaction (60.90%) (Table 2).

Pre-conception and early childhood health history

Odds of allergies were lower among children conceived via ART as compared to spontaneous conception (OR = 0.39, 95% CI: 0.17, 0.88) (Table 3). Children reported with biological mothers or fathers who were older had slightly higher odds

of allergies (OR = 0.97 95% CI: 0.92, 1.02 and OR = 0.94, 95% CI: 0.90, 1.00) respectively, for each additional year of age) (Table 3). Family history of allergies in either biological mother or father was also associated with higher odds of allergies in children (OR = 3.60, 95% CI: 2.08, 6.22 and OR = 2.67, 95% CI: 1.63, 4.39 respectively) (Table 3).

Post-conception health history in children

Most of the children in our study were reported to have been delivered vaginally, with or without induction, breastfed for at least 6 months, and had all of their childhood vaccinations (Table 4). Delivery by Cesarean was not associated with odds of allergies for either scheduled (OR = 1.66, 95%

Table 2 Specific allergy history of biological parents, if known, and child as reported by respondent

Allergy history	Child n/N (%)	Biological Mother n/N (%)	Biological Father n/N (%)
At least one reported	247 / 562 (43.95%)	358 / 563 (63.59%)	300 / 561 (53.48%)
Unknown/rather not respond	19 / 562 (3.38%)	11 / 563 (1.95%)	14 / 561 (2.50%)
Peanut	68 / 562 (12.10%)	17 / 563 (3.02%)	12 / 561 (2.14%)
Tree nuts	60 / 562 (10.68%)	19 / 563 (3.37%)	3 / 561 (0.53%)
Milk	43 / 562 (7.65%)	19 / 563 (3.37%)	15 / 561 (2.67%)
Eggs	41 / 562 (7.30%)	9 / 563 (1.60%)	4 / 561 (0.71%)
Soybean	16 / 562 (2.85%)	8 / 563 (1.42%)	3 / 561 (0.53%)
Wheat/gluten	11 / 562 (1.96%)	24 / 563 (4.26%)	6 / 561 (1.07%)
Shellfish	16 / 562 (2.85%)	23 / 563 (4.09%)	23 / 561 (4.10%)
Fruit	24 / 562 (4.27%)	28 / 563 (4.97%)	11 / 561 (1.96%)
Medicine/drugs	32 / 562 (5.69%)	115 / 563 (20.43%)	51 / 561 (9.09%)
Latex	5 / 562 (0.89%)	30 / 563 (5.33%)	8 / 561 (1.43%)
Insect stings (bees)	4 / 562 (0.71%)	22 / 563 (3.91%)	9 / 561 (1.60%)
Mold	36 / 562 (6.41%)	115 / 563 (20.43%)	44 / 561 (7.84%)
Pets/animals	60 / 562 (10.68%)	132 / 563 (23.45%)	113 / 561 (20.14%)
Pollen/hayfever	135 / 562 (24.02%)	238 / 563 (42.27%)	205 / 561 (36.54%)
Sesame	9 / 562 (1.60%)	0 / 0 (0.00%)	0 / 0 (0.00%)
Sensitizing Treatment			
No	120 / 134 (89.55%)		
Yes, current	14 / 134 (10.45%)		
Anaphylactic reactions			
None	81 / 133 (60.90%)		
1	22 / 133 (16.54%)		
2	17 / 133 (12.78%)		
3	6 / 133 (4.51%)		
4	1 / 133 (0.75%)		
5 or more	5 / 133 (3.76%)		
Unknown	1 / 133 (0.75%)		

Table 3 Pre-conception characteristics of biological parents, if known, by allergy status as reported by respondents

Characteristic	Allergies n/N (%)	No-Allergies n/N (%)	OR (95% CI) ^a
Method of conception			
Spontaneous	206 / 226 (91.15%)	268 / 316 (84.81%)	— ^b
ART	20 / 226 (8.85%)	48 / 316 (15.19%)	0.39 (0.17, 0.88)
Mean age biological parent at conception			
Father	32.84 (4.73, n = 219)	33.71 (4.89, n = 315)	0.94 (0.90, 1.00)
Mother	31.70 (4.47, n = 228)	32.16 (4.33, n = 316)	0.97 (0.92, 1.02)
Family History			
Biological mother with any allergies	181 / 237 (76.37%)	175 / 324 (54.01%)	3.60 (2.08, 6.22)
Biological father with any allergies	149 / 235 (63.40%)	141 / 325 (43.38%)	2.67 (1.63, 4.39)

a. Odds ratios (OR) and 95% confidence intervals (CI) calculated from a separate univariable Generalized Linear Mixed Model (GLMM) for each characteristic in the table. Each univariable GLMM was run as a mixed logistic regression model with a random intercept for household

b. Reference category

CI OR: 0.79, 3.70) or emergency (OR = 0.88, 95% CI OR: 0.44, 1.74) procedures, as compared to vaginal delivery with no induction. The odds of allergies were 9.93 times higher

in children with a history of asthma (95% CI for OR: 4.49, 21.96) and 11.92 times higher in children with a history of eczema (95% CI for OR: 5.75, 24.72) (Table 4). There was

Table 4 Delivery and childhood medical history as reported by allergy status

Characteristic	Allergies n/N (%)	No-Allergies n/N (%)	OR (95% CI) ^a
How was the child delivered?			
Vaginal delivery, no induction	87 / 228 (38.16%)	122 / 316 (38.61%)	— ^b
Vaginal delivery, induced	62 / 228 (27.19%)	94 / 316 (29.75%)	1.06 (0.58, 1.92)
C-section, scheduled	37 / 228 (16.23%)	37 / 316 (11.71%)	1.66 (0.76, 3.61)
C-section, emergency	42 / 228 (18.42%)	63 / 316 (19.94%)	0.88 (0.44, 1.74)
Was the child breastfed?			
No, only formula fed	14 / 225 (6.22%)	23 / 312 (7.37%)	0.72 (0.26, 2.01)
No, but supplemented with some breastmilk	32 / 225 (14.22%)	44 / 312 (14.10%)	1.08 (0.50, 2.31)
Yes, 1 to 3 months	22 / 225 (9.78%)	25 / 312 (8.01%)	1.13 (0.44, 2.89)
Yes, 3 to 6 months	22 / 225 (9.78%)	25 / 312 (8.01%)	1.27 (0.51, 3.18)
Yes, 6 to 12 months	57 / 225 (25.33%)	87 / 312 (27.88%)	0.89 (0.47, 1.68)
Yes, more than 12 months	78 / 225 (34.67%)	108 / 312 (34.62%)	— ^b
Allergy or sensitivity to breastmilk			
Yes	44 / 225 (19.56%)	43 / 312 (13.78%)	1.73 (0.94, 3.19)
Yes, to eggs	17 / 225 (7.56%)	16 / 312 (5.13%)	1.71 (0.67, 4.38)
Yes, to milk	17 / 225 (7.56%)	19 / 312 (6.09%)	1.42 (0.58, 3.44)
Yes, to wheat	3 / 225 (1.33%)	6 / 312 (1.92%)	0.55 (0.09, 3.36)
Yes, to soy/soybeans	7 / 225 (3.11%)	8 / 312 (2.56%)	1.38 (0.35, 5.40)
Other	8 / 225 (3.56%)	4 / 312 (1.28%)	4.11 (0.80, 21.15)
Vaccinated			
All	211 / 237 (89.03%)	303 / 326 (92.94%)	— ^b
Some or None	26 / 237 (10.97%)	23 / 326 (7.06%)	1.69 (0.72, 3.97)
Asthma	55 / 237 (23.21%)	12/234 (3.70%)	9.93 (4.49, 21.96)
Eczema	101 / 237 (42.62%)	36 / 324 (11.11%)	11.92 (5.75, 24.72)

a. Odds ratios (OR) and 95% confidence intervals (CI) calculated from a separate univariable GLMM for each characteristic in the table. Each univariable Generalized Linear Mixed Model (GLMM) was run as a mixed logistic regression model with a random intercept for household

b. Reference category

not sufficient evidence to suggest a significant difference in odds of allergies among children who were reported to have previously had an allergy or sensitivity to breastmilk (OR = 1.73, 95% CI: 0.94, 3.19) (Table 4).

Multivariable mixed logistic regression model

In our exploratory, full multivariable model, after adjusting for sociodemographic and reproductive and medical history characteristics, household income, allergy history of biological mother and father and age of child were the only characteristics still significantly associated with odds of allergies in children. After adjusting for all other variables in the model, the odds of allergies were 2.74 and 2.06 times higher for children whose biological mother or biological father, respectively, were reported to have a history of allergies (adj OR = 2.74, 95% CI: 1.59, 4.72 and adj OR = 2.06, 95% CI: 1.24, 3.41) (Table 5). For each additional year of age for the child, the odds of allergies increased by 17%, after controlling for all else in the model (adj OR = 1.17, 95% CI: 1.10, 1.24) (Table 5).

Children reported from households with an annual income of less than \$100,000 had higher adjusted odds of allergies than those from homes with an income of \$200,000 or more (Table 5). For those living in a household with an annual income of \$50,000 to \$99,999, the adjusted odds of allergies were 2.72 times higher (95%CI: 1.11, 6.65) than children reported living in a household with an annual income of \$200,000 or more (Table 5). For those with a household income of less than \$50,000, the adjusted odds of allergies were 1.55 times higher than reported children from homes with an income of \$200,000 or more, but the result was not statistically significant (95% CI: 0.37, 6.54) (Table 5). Mode of conception and community were no longer significantly associated with allergies after adjusting for other variables in the model. However, as this was an exploratory study, our multivariable results are still suggestive of lower odds of allergies in those children conceived by ART (adj OR = 0.55, 95% CI: 0.25, 1.20) and suggestive of higher odds of allergies in those children living in suburban rather than urban communities (adj OR = 1.66, 95% CI: 0.91, 3.04) (Table 5).

Table 5 Full multivariable mixed model results for study characteristics and allergy association

Characteristic	Beta	Adjusted OR ^a	95% CI ^a
Intercept	-3.36		
Conceived with ART vs Spontaneous	-0.60	0.55	(0.25, 1.20)
Breastfeeding			
Formula with some BF vs no BF	0.47	1.60	(0.55, 4.64)
BF 1–3 Months vs no BF	0.67	1.95	(0.60, 6.33)
BF 3–6 Months vs no BF	0.34	1.40	(0.43, 4.61)
BF 6–12 months vs no BF	0.32	1.38	(0.51, 3.77)
BF > 12 months vs no BF	0.34	1.41	(0.53, 3.74)
No BF allergies vs any BF allergy	-0.49	0.61	(0.33, 1.14)
Mode of delivery			
Induced vaginal vs vaginal	0.09	1.09	(0.60, 1.99)
Scheduled c-section vs vaginal	0.43	1.53	(0.72, 3.28)
Emergency/unsched c-section vs vaginal	-0.32	0.73	(0.37, 1.44)
Biological mother allergies vs none	1.01	2.74	(1.59, 4.72)
Biological father allergies vs none	0.72	2.06	(1.24, 3.41)
Community			
Suburban vs city	0.51	1.66	(0.91, 3.04)
Rural vs city	0.24	1.28	(0.42, 3.92)
Income ^b			
Less than \$50,000 vs \$200,000 or more	0.44	1.55	(0.37, 6.54)
\$50,000 – 99,999 vs \$200,000 or more	1.00	2.72	(1.11, 6.65)
\$100,000—149,999 vs \$200,000 or more	-0.48	0.62	(0.29, 1.29)
\$150,000 to 199,999 vs \$200,000 or more	0.36	1.43	(0.71, 2.87)
Did not respond vs \$200,000 or more	1.14	3.13	(0.74, 13.27)
Child's age	0.15	1.17	(1.10, 1.24)
Sex			
Female vs Males	-0.40	0.67	(0.42, 1.07)
Other vs Males	-0.14	0.87	(0.11, 6.65)
Vaccine Status			
Some or no vaccines vs All vaccines	0.02	1.02	(0.41, 2.51)
Race			
Black vs white	-0.56	0.57	(0.17, 1.94)
Asian Am/PI/AI/AN vs white	0.38	1.47	(0.55, 3.94)
Multiple vs white	0.25	1.28	(0.67, 2.45)
Respondent's Education			
Bachelor's degree vs less than a bachelor's degree	0.01	1.01	(0.32, 3.15)
More than bachelor's degree vs less than a bachelor's degree	0.78	2.17	(0.68, 6.93)

a. Adjusted odds ratios (OR) and 95% confidence intervals (CI) calculated from a single, full multivariable GLMM. The multivariable Generalized Linear Mixed Model (GLMM) was run as a mixed logistic regression model with a random intercept for household and each reported OR is adjusted for all other variables in the table

b. Nested model test for income had a *p*-value of 0.035

Discussion

To date, there have been few studies examining possible associations between specific parental allergy and reproductive health history and allergy prevalence in offspring.

Using GLMM with univariable mixed logistic regression models, age of child, history of asthma and eczema, mode of conception, community, age, household income, biological parent allergy status, and age of biological parent at conception were found to be significantly associated with

odds of allergies reported in children. In addition, a full multivariable mixed logistic regression model revealed that household income, biological parental allergies and age of child were significantly associated with odds of allergy in children after adjusting for other factors.

In our univariable analysis, older parental age was significantly associated with higher odds of allergies in children. This supports what has been previously reported in a cohort of 1344 singleton children in the Longitudinal Investigation of Global Health in Taiwanese Schoolchildren where increased maternal age was associated with increased odds of allergic conditions in children [15]. However, this differs from reports from the Danish National Birth Cohort, wherein asthma incidence, a common comorbidity of allergies, was lower among children with older biological fathers at time of delivery [16]. Multivariable analysis also revealed that allergy history in biological parents were associated with reported allergies in children, concurrent with previous studies which reported that children were significantly more likely to have an allergy if a biological parent also had an allergy [12, 29–31].

In addition, children who mainly resided in a suburban community had a higher odds of having an allergy than those living in an urban setting after adjusting for all other variables in the model. This is counter to the hygiene hypothesis that suggests that the microbes children encounter early in life in a rural setting protect against allergies in children later on in life [32]. However, there have been studies with conflicting results; for example, a study surveying 35,128 children between 2009–2011 found that those living in suburban centers had the highest prevalence of food allergy, which supports our findings and highlights the need for further research in a larger more representative study population [33].

Lower household income was observed to be associated with greater odds of reporting allergies in children. Past studies have also observed conflicting results when investigating allergies, allergic diseases, and socioeconomic background [34–36]. High socioeconomic status seemed to prevent children from developing atopic disorders, while children living in a lower-income household had an increased odds of developing the allergic condition atopic dermatitis [34, 35, 37].

Of the top six most commonly reported allergies in children, four were food-related, compared to only two of the top six allergies were food-related among biological mothers or fathers. This difference reflects global trends, whereby childhood food allergies have been increasing [4]. When specifically focusing on the reported food allergies in both children and their biological parents, there was an increase in the number of peanut and tree nut allergies reported between biological parents and children, consistent with trends observed over the last few decades [38–40].

Our work further contributes to the studies that have investigated allergies in children using ART. Among the 3–20 year old twin pairs reported in the Danish Twin Registry, there was no difference in the odds of having atopic outcomes in twins conceived spontaneously or using ART [41]. A study examining allergic conditions in 158 children conceived with IVF and 102 children conceived spontaneously who were born in an international hospital between 2002–2004 found no significant difference in the incidence of asthma, allergic rhinitis, atopic dermatitis, and environmental allergies between the two groups [42]. In contrast, a cohort study investigating health outcomes in 705 ART conceived young adults and 549 non-ART conceived young adults in Australia found that ART conceived young adults had a significant increase in environmental allergies and asthma when compared to the non-ART conceived group [43]. In addition, findings from the Upstate KIDS cohort found that children reported between 7–9 years old conceived with infertility treatment were more likely to be prescribed allergy medicine, to have any atopy or asthma than those conceived without ART treatment [21]. Results from these cohort studies were supported by a study investigating the cytokine levels and immune cell profile of the peripheral blood collected from 69 children born with ART and 17 children conceived spontaneously, which found that children born using ART had an altered immune profile, specifically higher interferon- γ levels, which is associated with allergic pathologies [20, 44].

In the current study, analysis with GLMM using univariable mixed logistic regression models observed that children conceived spontaneously had a higher odds of allergy history than those conceived using ART. Our results, which were counter to our initial expectations, may indicate that removing the gamete or embryo from the maternal uterine environment during a certain time period through specific ART techniques may protect offspring from developing an allergy. Perhaps this is due to key epigenetic changes that occur early on that may influence the developing immune system, as it has been found that specific in utero environmental exposures may modify the developing immune system of the fetus [45]. Of note, our study lacks data on or adjustment for factors, including high birth weight relative to the gestational age of the child, maternal gestational diabetes, and advanced maternal age in our model, which have all been found to be associated with increased odds and/or risk of allergy in children [22, 46–49]. In addition, we did not collect certain data on ART treatments, including frozen embryo transfer which impacts the immune profile of children conceived using ART [20]. This highlights a connection between parental reproductive health history, specifically mode of conception, and allergies in children, and emphasizes a need for more comprehensive follow up studies to better understand these findings in context of previous

studies. Data reported on specific ART were too small to meaningfully disaggregate types of ART in analysis or interpretation of findings, so we did not differentiate between ART procedures that involve removing the gamete from the uterine environment vs those that do not.

Interestingly using both univariable and multivariable analysis we found that, while not significant, children born via emergency Cesarean section tended to have a lower odds of developing an allergy than those born vaginally. Previous studies in microbiome research have reported that the lack of exposure to the maternal birth canal microbes through Cesarean section could impact the developing immune system of the newborn, but results are conflicting [50–56]. A cohort study of 24,690 children from the West Midlands General Practice Research Database and a study of 279 Korean children under the age of 16 found that the mode of delivery had no impact on allergy disease in children [50, 53]. Meanwhile, children born via Cesarean section in the Oslo Birth cohort were more likely to have food allergies than those not born via Cesarean section [51]. In addition, a study conducted in the Upstate KIDS cohort found that emergency Cesarean section was associated with an increased risk of wheeze and food allergy when compared to vaginally delivered children [52]. In the current study, we did not collect data on fetal birth weight or prenatal antibiotic exposure in our study population, which could account for why our results conflict with what has been published previously [47, 57]. Children conceived using IVF/ICSI are more likely to be born via Cesarean section, and therefore this in itself may explain the lower odds of allergy observed in children born by Cesarean section in our population [58].

There are several limitations to the current exploratory study. The use of a survey instrument distributed via convenience, snowball sampling increased the risk of selection bias. Due to the exploratory nature of this study and the small sample size of our population, there was a risk of sampling bias, reflected by the majority of our respondents who were highly formally educated, white, and from a high socioeconomic background. Given the convenience, snowballing technique utilized to recruit respondents, study findings are limited in their ability to be extrapolated to the general or wider proportion of the population. However, as an exploratory study, these findings introduce initial associations that warrant further study and highlight the need for continued research in this area.

The design of an anonymous survey also limits the data that can be collected from a respondent as well as the possibility of follow-up or clarification. In addition, respondents were also asked questions about each of their children under 18 years of age, which is sensitive to recall bias. Some questions in the survey were also left open ended or left with the option to answer an open ended

question under the category of other, which may have led to interpretation bias. However, this was minimized by close qualitative data analysis prior to quantitative analysis and modeling.

In the future, retrospective and prospective approaches would be needed to further explore the associations and trends these data have revealed. A reasonable next step would be to explore a case–control analysis with recruitment of children from allergy clinics to serve as cases, and a randomized sample of controls from local pediatric practices with similar socioeconomic backgrounds. Electronic medical records with de-identified data would be used to compare mode of conception and breastfeeding and delivery history as reported at the time. A large medical network with linked medical records, such as Duly Health would serve as a cohesive EMS to provide data. Ultimately, the best future study would be to design a longitudinal study that recruits couples using ART at the time of fertility treatments and expecting parents using spontaneous conception to compare the parental histories, perinatal and prenatal histories, and to follow-up on offspring from birth to age 18 to identify allergy outcomes and puberty outcomes. Despite the limitations of this initial exploratory study, these findings provide novel insights into reproductive health and allergy history of biological parents and children, and follow up studies are warranted to further investigate this connection.

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Author contributions Susan Cheng, Francesca Duncan, and Mary Ellen Pavone conceived of the study and its design. Material preparation, data collection and analysis were performed by Madison Gowett, Sarah Perry, Raveena Aggarwal, Luhan Zhou, Susan Cheng and Francesca Duncan. Madison Gowett and Sarah Perry wrote the manuscript, and Susan Cheng, Francesca Duncan, and Mary Ellen Pavone provided editorial and intellectual feedback. All authors read and approved the final manuscript.

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Data Availability The programs and datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval The questionnaire and methodology for this study was approved by the Institutional Review Board at Northwestern University (IRB Study Number: STU00211102).

Consent to participate Informed consent was obtained from legal guardians.

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